Electronic Supplementary Information

**Tromethamine Organocatalyzed Efficient Tandem-Multicomponent Synthesis of New Thiazolyl-4-Thiazolidinones in Aqueous Medium**

Manisha R. Bhosle,a\* Sayali A. Kharote,a Giribala M. Bondle,a Jyotirling R. Malib

aDepartment of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431004, Maharashtra, India

bCollege of Pharmacy, Dongguk University-Seoul, Goyang-10326, Republic of Korea.

*E-mail:* *d.manisha11@gmail.com*

**Table of contents**

**1.General Information.....................................................................................................S2**

**2.Experimental Procedures.............................................................................................S2**

**3. Characterization Data for the Products.......................................................................S3-S6**

**4. Copies of IR and 1H NMR Spectra of the Products ………………………………….S7-S11**

**Materials and methods**

**General:** All the chemicals used were of laboratory grade. Melting points of all the synthesized compounds were determined in open capillary tubes and are uncorrected. 1H NMR spectra were recorded with a Bruker Avance 400 spectrometer operating at 400 MHz using DMSO solvent and tetramethylsilane (TMS) as the internal standard and chemical shift in δ ppm. Mass spectra were recorded on a Sciex, Model; API 3000 LCMS/MS Instrument. The elemental analysis was done on Thermofisher EA1112 series CHNS Elemental Analyser. The purity of each compound was checked by TLC using silica-gel, 60F254 aluminum sheets as adsorbent and visualization was accomplished by iodine/ultraviolet light.

**General Procedure for the Synthesis of 3-(substituted phenyl)-2-(4-((2-phenylthiazol-4-yl)methoxy) phenyl) thiazolidin-4-ones (3a-l)**

The mixture of 4-((2-phenylthiazol-4-yl)methoxy)benzaldehyde **(1)** (4 mmol) and substituted anilines (**2a-l)** (4.1 mmol) in water (20 ml) containing tris-hydroxymethylaminomethane (Tromethamine) (30 mol%) was stirred at 80 °C for 15 min. Then thioglycolic acid (8 mmol) was added and stirred at 80 ̊C. Progress of the reaction was monitored by thin layer chromatography ethyl acetate:hexane (3:7) as solvent. After 45 min. of stirring reaction mixture was cooled at room temperature, saturated sodium bicarbonate was added till gate pink color, to remove thioglycolic acid. Sticky compound was extracted with ethyl acetate and evaporated organic layer under reduced pressure. Thus obtained solid was filtered, dried and purified by crystallization using ethanol as solvent.

**Recycling of reaction media**

The mixture of 4-((2-phenylthiazol-4-yl)methoxy)benzaldehyde **(1)** (8 mmol) and anilines (**2a)** (8 mmol) in water (40 ml) containing tris-hydroxymethylaminomethane (Tromethamine) (30 mol%) was stirred at 80 °C for 15 min. Then thioglycolic acid (16 mmol) was added and stirred at 80 ̊C. Progress of the reaction was monitored by thin layer chromatography ethyl acetate:hexane (3:7) as solvent. After 45 min. of stirring reaction mixture was cooled at room temperature. Sticky compound was extracted with ethyl acetate and evaporated organic layer under reduced pressure. The aqueous layer having soluble tromethamine was further reused for next cycle.

**Spectral analysis of compounds**

**3-Phenyl-2-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)thiazolidin-4-one (3a)**

Yellow solid, Yield 82%. Melting point 146-148 ºC. **IR (**ATR, υ cm-1**)** Characteristic absorptions: 3250, 3193, 3076, 2888, 2343, 1641, 1480, 1490, 1325, 1171, 947, 747. 1H NMR (400 MHz, DMSO δppm):4.37-4.43 (dd, 2H, CH2), 5.20 (s, 2H, CH2), 6.08 (s, 1H, CH), 7.38-7.51 (m, 2H, Ar-H), 7.55-7.70 (m, 4H, Ar-H), 7.77-7.96 (m, 4H, Ar-H), 8.04-8.46 (m, 5H, Ar-H). **MS** (Scanning mode, ESI+) m/z: 445.5 (M+). Elemental Anal. calcd. for C25H20N2O2S2: C: 67.54; H: 4.53; N: 6.30; S: 14.43; Found: C: 67.53; H: 4.55; N: 6.37; S: 14.41.

**3-(4-Methylphenyl)-2-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)thiazolidin-4-one (3b)**

Off White solid, Yield 79%. Melting point 98-100 ºC. **IR (**ATR, υ cm-1**)** Characteristic absorptions: 3365, 3185, 2850, 2312, 1652, 1447, 1108, 833, 754. 1H NMR (400 MHz, DMSO δppm): 2.85 (s, 3H, CH3), 4.36-4.40 (dd, 2H, CH2), 5.24 (s, 2H, CH2), 6.25 (s, 1H, CH), 7.30-7.40 (m, 3H, Ar-H), 7.52-7.57 (m, 4H, Ar-H), 7.72-7.75 (m, 2H, Ar-H), 7.87-8.0 (m, 6H, Ar-H). **MS** (Scanning mode, ESI+) m/z: 459 (M+). Elemental Anal. calcd. for C26H22N2O2S2: C: 68.09; H: 4.84; N: 6.11; S: 13.98; Found: C: 68.12; H: 4.81; N: 6.18; S: 14.00

**3-(4-Methoxyphenyl)-2-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)thiazolidin-4-one (3c)**

Pale Yellow solid, Yield 81%. Melting point 134-136 ºC. **IR (**ATR, υ cm-1**)** Characteristic absorptions: 3127, 2869, 1751, 1655, 1437, 1267, 1039, 805, 723. 1H NMR (400 MHz, DMSO δppm): 3.83 (s, 3H, OCH3), 4.36-4.40 (dd, 2H, CH2), 5.23 (s, 2H, CH2), 6.05 (s, 1H, CH), 7.05-7.07 (m, 3H, Ar-H), 7.14-7.25 (m, 3H, Ar-H), 7.35-7.40 (m, 3H, Ar-H), 7.52-7.99 (m, 5H, Ar-H). **MS** (Scanning mode, ESI+) m/z: 475 (M+). Elemental Anal. calcd. for C26H22N2O3S2: C: 65.80; H: 4.67; N: 5.90; S: 13.51; Found: C: 65.86; H: 4.61; N: 5.93; S: 13.52.

**3-(4-Clorophenyl)-2-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)thiazolidin-4-one (3d)**

Yellow solid, Yield 89%. Melting point 103-105 ºC. **IR (**ATR, υ cm-1**)** Characteristic absorptions: 3043, 2852, 1744, 1602, 1250, 1034, 830, 753. 1H NMR (400 MHz, DMSO δppm): 4.36-4.43 (dd, 2H, CH2), 5.21 (s, 2H, CH2), 6.04 (s, 1H, CH), 7.23-7.37 (m, 4H, Ar-H), 7.52-7.59 (m, 3H, Ar-H), 7.71-7.97 (m, 4H, Ar-H), 8.20-8.51 (m, 3H, Ar-H). **MS** (Scanning mode, ESI+) m/z: 480 (M+). Elemental Anal. calcd. for C25H19ClN2O2S2: C: 62.68; H: 4.00; N: 5.85; S: 13.39; Found: C: 62.61; H: 4.07; N: 5.84; S: 13.41.

**3-(4-Bromophenyl)-2-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)thiazolidin-4-one (3e)**

Yellow solid, Yield 80%. Melting point 107-109 ºC. **IR (**ATR, υ cm-1**)** Characteristic absorptions: 3156, 2851, 1738, 1675, 1257, 1038, 827, 745. 1H NMR (400 MHz, DMSO δppm): 4.37-4.44 (dd, 2H, CH2), 5.23 (s, 2H, CH2), 6.05 (s, 1H, CH), 7.21-7.35 (m, 4H, Ar-H), 7.50-7.58 (m, 3H, Ar-H), 7.69-7.87 (m, 4H, Ar-H), 7.91-8.23 (m, 3H, Ar-H). **MS** (Scanning mode, ESI+) m/z: 524 (M+). Elemental Anal. calcd. for C25H19BrN2O2S2: C: 57.36; H: 3.66; N: 5.35; S: 12.25; Found: C: 57.39; H: 3.63; N: 5.37; S: 12.25.

**3-(4-Flurophenyl)-2-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)thiazolidin-4-one (3f)**

Yellow solid, Yield 76%. Melting point 121-123 ºC. **IR (**ATR, υ cm-1**)** Characteristic absorptions: 3342, 3157, 2855, 1740, 1609, 1256, 1075, 858, 732. 1H NMR (400 MHz, DMSO δppm): 4.36-4.43 (dd, 2H, CH2), 5.25 (s, 2H, CH2), 6.05 (s, 1H, CH), 7.15-7.25 (m, 2H, Ar-H), 7.32-7.39 (m, 2H, Ar-H), 7.49-7.54 (m, 3H, Ar-H), 7.68-7.76 (m, 3H, Ar-H), 7.95-8.07 (m, 4H, Ar-H). **MS** (Scanning mode, ESI+) m/z: 463 (M+). Elemental Anal. calcd. for C25H19FN2O2S2: C: 64.91; H: 4.14; N: 6.06; S: 13.86 Found: C: 64.97; H: 4.15; N: 6.01; S: 13.89.

**4-(4-oxo-2-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)thiazolidin-3-yl)benzenesulfonamide (3g)**

Yellow solid, Yield 86%. Melting point 187-189 ºC. **IR (**ATR, υ cm-1**)** Characteristic absorptions: 3264, 3176, 3074, 2875, 2357, 1723, 1608, 1486, 1321, 1089, 841, 746. 1H NMR (400 MHz, DMSO δppm):4.37-4.44 (dd, 2H, CH2), 5.21 (s, 2H, CH2), 6.06 (s, 1H, CH), 7.29-7.48 (m, 4H, Ar-H), 7.51-7.69 (m, 4H, Ar-H), 7.72-7.81 (m, 2H, Ar-H), 7.92-8.02 (m, 4H, Ar-H). **MS** (Scanning mode, ESI+) m/z: 524 (M+). Elemental Anal. calcd. for C25H21N3O4S3: C: 57.34; H: 4.04; N: 8.02; S: 18.37; Found: C: 57.38; H: 4.09; N: 8.04; S: 18.40.

**3-(2,4-Dimethylphenyl)-2-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)thiazolidin-4-one (3h)**

Pale Yellow solid, Yield 80%. Melting point 154-156 ºC. **IR (**ATR, υ cm-1**)** Characteristic absorptions: 3365, 3185, 2850, 2312, 1652, 1447, 1108, 833, 754. 1H NMR (400 MHz, DMSO δppm): 2.26 (s, 3H, CH3), 2.42 (s, 3H, CH3), 4.37-4.42 (dd, 2H, CH2), 5.20 (s, 2H, CH2), 6.06 (s, 1H, CH), 7.32-7.40 (m, 2H, Ar-H), 7.48-7.56 (m, 4H, Ar-H), 7.71-7.74 (m, 2H, Ar-H), 7.84-7.96 (m, 6H, Ar-H). **MS** (Scanning mode, ESI+) m/z: 473 (M+). Elemental Anal. calcd. For C27H24N2O2S2: C: 68.61; H: 5.12; N: 5.93; S: 13.57; Found: C: 68.65; H: 5.16; N: 5.98; S: 13.61.

**3-(2-Methoxyphenyl)-2-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)thiazolidin-4-one (3i)**

Yellow solid, Yield 86%. Melting point 143-144 ºC. **IR (**ATR, υ cm-1**)** Characteristic absorptions: 3175, 2854, 1746, 1650, 1436, 1254, 1138, 1040, 854, 787. 1H NMR (400 MHz, DMSO δppm): 3.87 (s, 3H, OCH3), 4.36-4.41 (dd, 2H, CH2), 5.21 (s, 2H, CH2), 6.07 (s, 1H, CH), 7.12-7.18 (m, 2H, Ar-H), 7.21-7.27 (m, 3H, Ar-H), 7.34-7.45 (m, 4H, Ar-H), 7.51-7.87 (m, 5H, Ar-H). **MS** (Scanning mode, ESI+) m/z: 475 (M+). Elemental Anal. calcd. for C26H22N2O3S2: C: 65.80; H: 4.67; N: 5.90; S, 13.51; Found: C: 65.84; H: 4.70; N: 5.95; S, 13.52.

**3-(2-Hydroxyphenyl)-2-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)thiazolidin-4-one (3j)**

Yellow solid, Yield 89%. Melting point 136-137 ºC. **IR (**ATR, υ cm-1**)** Characteristic absorptions: 3421, 3132, 2854, 1730, 1643, 1251, 1038, 836, 758. 1H NMR (400 MHz, DMSO δppm): 4.37-4.45 (dd, 2H, CH2), 5.25 (s, 2H, CH2), 6.05 (s, 1H, CH), 7.26-7.39 (m, 4H, Ar-H), 7.51-7.59 (m, 3H, Ar-H), 7.73-7.95 (m, 4H, Ar-H), 7.99-8.14 (m, 3H, Ar-H). **MS** (Scanning mode, ESI+) m/z: 461 (M+). Elemental Anal. calcd. for C25H20N2O3S2: C: 65.20; H: 4.38; N: 6.08; S: 13.92; Found: C: 65.24; H: 4.31; N: 6.07; S: 13.99.

**2-(4-((2-Phenylthiazol-4-yl)methoxy)phenyl)-3-(pyridin-2-yl)thiazolidin-4-one (3k)**

Yellow solid, Yield 82%. Melting point 157-159 ºC. **IR (**ATR, υ cm-1**)** Characteristic absorptions: 3335, 3137, 2853, 1737, 1642, 1256, 1037, 833, 751. 1H NMR (400 MHz, DMSO δppm): 4.36-4.44 (dd, 2H, CH2), 5.22 (s, 2H, CH2), 6.08 (s, 1H, CH), 7.37-7.49 (m, 2H, Ar-H), 7.51-7.59 (m, 2H, Ar-H), 7.71-7.86 (m, 4H, Ar-H), 7.98-8.18 (m, 2H, Ar-H) 8.34-8.62 (m, 4H, Ar-H). **MS** (Scanning mode, ESI+) m/z: 446 (M+). Elemental Anal. calcd. for C24H19N3O2S2: C: 64.70; H: 4.30; N: 9.43; S: 14.39; Found: C: 64.75; H: 4.32; N: 9.44; S: 14.43.

**N-(4-Oxo-2-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)thiazolidin-3-yl)isonicotinamide (3l)**

Yellow solid, Yield 87%. Melting point 176-178 ºC. **IR (**ATR, υ cm-1**)** Characteristic absorptions: 3361, 3034, 2806, 2314, 1658, 1597, 1450, 1232, 1109, 992, 831, 764. 1H NMR (400 MHz, DMSO δppm): 4.37-4.43 (dd, 2H, CH2), 5.25 (s, 2H, CH2), 6.07 (s, 1H, CH), 7.32-7.50 (m, 2H, Ar-H), 7.51-7.58 (m, 2H, Ar-H), 7.72-7.88 (m, 4H, Ar-H), 7.96-8.20 (m, 2H, Ar-H) 8.32-8.60 (m, 4H, Ar-H). **MS** (Scanning mode, ESI-): m/z (% intensity): 487 (M-). Elemental Anal. calcd. For C25H20N4O3S2: C: 61.46; H: 4.13; N: 11.47; S: 13.13; Found: C: 61.44; H: 4.12; N: 11.50; S: 13.19.

**General Procedure for the Synthesis of 1,3-disubstituted-4-thiazolidinones (5a-l)** [1,2].

The mixture of substituted aldehydes **(4a-f)** (4 mmol) and substituted anilines (**2a-b)** (4.1 mmol) in water (20 ml) containing tris-hydroxymethylaminomethane (Tromethamine) (30 mol%) was stirred at 80 °C for 15 min. Then thioglycolic acid (8 mmol) was added and stirred at 80 ̊C. Progress of the reaction was monitored by thin layer chromatography ethyl acetate:hexane (3:7) as solvent. After 45 min. of stirring reaction mixture was cooled at room temperature, saturated sodium bicarbonate was added till gate pink color, to remove thioglycolic acid. Sticky compound was extracted with ethyl acetate and evaporated organic layer under reduced pressure. Thus obtained solid was filtered, dried and purified by crystallization using ethanol as solvent.

Synthesized compounds characterized by IR, 1H NMR and Melting points are in good agreement with those reported in the literature [1,2].

**3-Phenyl-2-(4-tolyl)thiazolidin-4-one (5b)** [1,2].

White solid, Yield 89%. Melting point 103-105 ºC. **IR (**ATR, υ cm-1**)** Characteristic absorptions: 3202, 2975, 2827, 2357, 1725, 1453, 1149, 1008, 857, 759. 1H NMR (400 MHz, DMSO δppm): 2.26 (s, 3H, CH3), 3.83-4.02 (dd, 2H, CH2), 5.99 (s, 1H, CH), 7.01-7.29 (m, 9H, Ar-H). **MS** (Scanning mode, ESI+): m/z (% intensity): 270 (M+). Elemental Anal. calcd. For C16H15NOS: C: 71.34; H: 5.61; N: 5.20; S: 11.90; Found: C: 71.35; H: 5.60; N: 5.25; S: 11.93.

**IR of Compound (3a)**



**1H NMR of Compound (3a)**



**IR of Compound (3b)**



**1H NMR of Compound (3b)**



**IR of Compound (3c)**



**1H NMR of Compound (3c)**



**IR of Compound (3d)**



**1H NMR of Compound (3d)**



**IR of Compound (5b)**



**1H NMR of Compound (5b)**



**References**

1. (a) Harale, R. R.; Shitre, P. V.; Sathe, B. R.; Shingare, M. S. *Res Chem Intermed*. **2016**, *42*, 6695; (b) Chaudhari, M. A.; Gujar, J. B.; Kawade, D. S.; Shinde, P. V.; Shingare, M. S. *Res Chem Intermed.* **2015**, *41*, 10027.
2. Pratap, U. R.; Jawale, D. V.; Bhosle, M. R.; Mane, R. A. *Tetrahedron Lett*. **2011**, *52*, 1689